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WPI Acc No: 1983-49522K/**198321**

Related WPI Acc No: 1985-191419

XRAM Acc No: C83-048113

**N-aminoacyl-azabicyclooctane carboxylic acid derivs. -
useful as hypotensives, and their intermediates**

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Number of Countries: 028 Number of Patents: 056

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
EP 79022	A	19830518	EP 82110070	A	19821102	198321 B
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AU 8290145	A	19830512				198326
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			JP 9177209	A	19821104
DK 9201144	A	19920917	DK 824904	A	19821104 199252
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JP 93031544	B	19930512	JP 82192622	A	19821104 199322
DK 166624	B	19930621	DK 824904	A	19821104 199330
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			JP 8690187	A	19821104
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CZ 9104162	A3	19930915	CS 914162	A	19911230 199346
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			JP 9177209	A	19821104
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Priority Applications (No Type Date) : DE 3226768 A 19820717; DE 3143946 A 19811105

Cited Patents: 6.Jnl.Ref; DE 1955375; EP 37231; JP52039020; JP52116485; No-SR.Pub; 00 4.Jnl.

Patent Details:

Patent No	Kind	Lan Pg	Main IPC	Filing Notes
EP 79022	A	G 37		
			Designated States (Regional) :	AT BE CH DE FR GB IT LI LU NL SE
EP 79022	B	G		
			Designated States (Regional) :	AT BE CH DE FR GB IT LI LU NL SE
US 5053519	A	9		
US 5061722	A	9		
JP 4217949	A	10 C07C-237/06	Div ex application	JP 8690187
DK 9201144	A	C07D-209/52	Div ex application	DK 824904
JP 93031544	B	6 C07D-209/52	Based on patent	JP 58103364
DK 166624	B	C07K-005/06	Previous Publ. patent	DK 8204904
JP 93059105	B	11 C07D-209/52	Div ex application	JP 82192622
			Based on patent	JP 62000051
JP 93065508	B	7 C07D-209/52	Div ex application	JP 82192622
			Based on patent	JP 2104573
JP 94094443	B2	10 C07C-227/08	Div ex application	JP 8690187
			Based on patent	JP 4217949
DK 172751	B	C07D-209/52	Previous Publ. patent	DK 9201144
CZ 9104162	A3	C07D-209/52		

Abstract (Basic): EP 79022 A

Azabicyclooctane derivs. of formula (I) and their physiologically acceptable salts are new: (Hydrogen atoms at ring positions 1 and 5 are cis to each other and the 3-carboxy gp. has the endo orientation. R1 is H, allyl, vinyl or the side chain of an opt. protected naturally occurring alpha-amino acid. R2 is H, 1-6C alkyl, 2-6C alkenyl or aryl (1-4C alkyl). Y is H or hydroxy and Z is H, or Y and Z are together oxygen. X is 1-6C alkyl, 2-6C alkenyl, 5-9C cycloalkyl, 6-12C aryl (opt. substd. 1-3 times by 1-4C alkyl or alkoxy, hydroxy, halo, nitro, amino (opt. substd. by 1 or 2 1-4C alkyl), or methylenedioxy) or indol-3-yl).

Also new are the intermediates (IIIA) and (IIIB), and their salts,

(W is H, 1-6C alkyl or 7-8C aralkyl; W' is a gp. removable by hydrogenolysis, acid or base; and R2 is not benzyl or p-nitrobenzyl if W' is benzyl).

(I) have a strong and long-lasting hypotensive action (by inhibition of angiotensin-converting enzyme). Unit doses usually contain 1-100 mg.

Abstract (Equivalent): EP 79022 B

Azabicyclooctane derivs. of formula (I) and their physiologically acceptable salts are new: (Hydrogen atoms at ring positions 1 and 5 are cis to each other and the 3-carboxy gp. has the endo orientation. R1 is H, allyl, vinyl or the side chain of an opt. protected naturally occurring alpha-amino acid. R2 is H, 1-6C alkyl, 2-6C alkenyl or aryl (1-4C alkyl). Y is H or hydroxy and Z is H, or Y and Z are together oxygen. X is 1-6C alkyl, 2-6C alkenyl, 5-9C cycloalkyl, 6-12C aryl (opt. substd. 1-3 times by 1-4C alkyl or alkoxy, hydroxy, halo, nitro, amino (opt. substd. by 1 or 2 1-4C alkyl), or methylenedioxy) or indol-3-yl).

Also new are the intermediates (IIIA) and (IIIB), and their salts, (W is H, 1-6C alkyl or 7-8C aralkyl; W' is a gp. removable by hydrogenolysis, acid or base; and R2 is not benzyl or p-nitrobenzyl if W' is benzyl).

(I) have a strong and long-lasting hypotensive action (by inhibition of angiotensin-converting enzyme). Unit doses usually contain 1-100 mg. (37pp)

Abstract (Equivalent): US 5061722 A

Cis-endo-2-azabicyclo-(3.3.0)-octane-3-carboxylic acids of formula (I) and their salts are new. R2 = H, CH₃, C₂H₅ or benzyl. The H atoms on the ring C atoms in the 1- and 5-posns. are in the cis configuration w.r.t. each other, the CO₂H gp. on ring C atom in the 3-posn. is in the endo posn. w.r.t. the bicyclic ring system and the chirality centres all have the S-configuration.

N-(1-S-carboethoxy-3-phenyl-propyl)-S-alanyl-cis-endo-2-azabicyclo-(3.3.0)-octane-3-S-carboxylic acid is specifically claimed.

USE - As hypotensives (claimed).

US 5053519 A

A mixt. of enantiomers of cis-endo-2-azabicyclo-(3.3.0)-octane-3-carboxylic acid esters of formula (Ia) and (Ib) or their salts with acids or bases is new. In the formulae, W = H, 1-6C alkyl or 7-8C aralkyl. (Ia) and (Ib) may be prepared from cyclopentanone enamines of formula (II) and N-acylated beta-halo-alpha-amino carboxylic acid esters of formula (III). In (II) X₁ = 2-10C dialkylamino or gp. (IV) where m and p = 1-3 and m+p = 3 or more and A = CH₂, NH, O or S. In (III) X₂ = a nucleofugic gp., e.g. Cl or Br, Y₁ = 1-5C alkanoyl, 7-9C aroyl or another protective gp. customary in peptide chemistry which can be split off under acid conditions and R₂ = 1-5C alkyl or 7-9C aralkyl.

USE - As intermediates for cis, endoazabicyclo-(3.3.0)-octane carboxylic acids useful as hypotensive agents. (9pp)c

US 4879403 A

A cpd. X-CO-CH₂-C'H(COOR')-NH-C'H(R)-COOQ is produced by reacting an S-alpha-amino acid ester H₂N-C'H(R)-COOQ with a keto-acrylic acid ester X-CO-CH=CH-COOR' to obtain a mixt contg mainly the desired cpd, isolating the desired cpd. by crystallisation and pref. removing Q by hydrogenolysis.

In the formulae the chiral centres C' have the S configuration; R is Me or 4-amino-butyl both opt. acylated; R' is 1-6C alkyl, pref. Me

or Et; X is R', 2-6C alkenyl, 5-9C cycloalkyl or 6-12C aryl all opt 1-3 times subst. by 1-4C alkyl or alkoxy or alkylamino, OH, halogen, NO₂, NH₂, di(1-4C) alkylamino and/or methylenedioxy or is indole-3-yl; Q is an esterifying gp removable by hydrogenolysis. X is esp Ph opt. 1-2 times subst. by F and/or Cl.

USE/ADVANTAGE - Used to control high blood pressure; the cpd. has a long lasting, intense hypotensive action and can be given orally or perenterally. (9pp),

US 4727160 A

New cis, endo-2-azabicyclo(3,3,0)-octane-3- carboxylic acid esters of formulae (IIIa) and (IIIb) and salts, can be made by new process comprising cyclising (X) to intermediate (XIa) and (XIb) and catalytic hydrogenation or redn. (X) are obt. by reacting cyclopentanone enamine (VI), or radical (VII) and N-acylated beta-halogeno-alpha amino carboxylic acid esters (VIII). W is H, 1-6C alkyl, 7-8C aralkyl; Y is 1-5C alkanoyl, 7-9C aroyl; R₂ is 1-5C alkyl, 7-9C aralkyl, X₁ is 2-10C dialkylamino or (A) where m and o are each 1-3; (m + o) is 3; A is CH₂, NH, O or S; X₂ is Cl, Br or acrylic acid (B).

USE - Intermediate to cis, endoazabicyclo(3,3,0)-octane carboxylic acid of formula (I) by reacting (II) with (IIIa) or (IIIb). R₁ is H, vinyl, allyl, or side chain of alpha amino acid R₁-CH(NH₂)COOH. Y is H or OH; Z is H, or Y and Z together are O; X is 1-6C alkyl, 2-6C alkenyl, 5-9C cycloalkyl 6-12C aryl, opt. subst. (I) are ACE-inhibitors used as long-lasting hypotensives at dosages eg. 13-1300 (13-400) mcg/kg/day p.o. Low toxicity. (9pp)

Title Terms: N; AMINO; ACYL; AZA; BI; CYCLOOCTANE; CARBOXYLIC; ACID; DERIVATIVE; USEFUL; HYPOTENSIVE; INTERMEDIATE

Derwent Class: B02

International Patent Class (Main): C07C-227/08; C07C-237/06; C07D-209/52; C07K-005/06

International Patent Class (Additional): A61K-031/40; A61K-031/405; A61K-037/02; C07C-099/00; C07C-101/28; C07C-103/52; C07C-227/10; C07C-227/14; C07C-227/16; C07C-229/28; C07C-229/36; C07D-029/02; C07D-317/48; C07D-317/60; C07D-403/12; C07D-405/12; C07D-451/04; C07K-001/02; C07K-005/12

File Segment: CPI

Manual Codes (CPI/A-N): B06-A02; B06-D01; B06-D04; B10-B02B; B12-F05; B12-G01; N05-C

Chemical Fragment Codes (M2):

01 D011 D013 D019 D020 D021 D140 D601 D690 D699 F014 F521 G002
G010 G011 G012 G013 G014 G015 G016 G017 G019 G030 G040 G050 G100
G111 G112 G553 G563 G573 G583 H1 H100 H101 H102 H103 H141 H142 H143
H181 H182 H2 H211 H341 H342 H343 H401 H402 H403 H404 H405 H421 H441
H442 H443 H444 H481 H482 H498 H541 H542 H543 H600 H601 H602 H603
H608 H609 H641 H642 H643 H713 H714 H716 H721 H722 H723 J0 J013 J014
J1 J111 J171 J172 J271 J3 J371 J372 J581 L250 L432 M210 M211 M212
M213 M214 M215 M216 M231 M232 M233 M240 M262 M272 M273 M280 M281
M282 M283 M311 M312 M313 M314 M315 M316 M321 M322 M323 M331 M332
M333 M340 M342 M343 M344 M349 M371 M373 M381 M391 M392 M412 M511
M512 M513 M520 M521 M530 M531 M532 M533 M540 M541 M630 M640 M650
M710 M800 M903 P526 P616 V814

02 D012 D690 G010 G100 J0 J011 J111 J211 M210 M211 M212 M213 M214 M215
M216 M231 M232 M233 M272 M280 M281 M311 M312 M320 M321 M331 M332
M340 M342 M373 M391 M412 M511 M520 M530 M531 M540 M630 M640 M650
M710 M800 M903

03 D011 D019 D020 D021 D022 D140 D601 D699 F014 F521 G002 G010 G011
G012 G013 G014 G015 G016 G017 G019 G030 G040 G050 G100 G111 G112

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H182 H341 H342 H343 H401 H402 H403 H404 H441 H442 H443 H444 H481
H498 H541 H542 H543 H600 H601 H602 H603 H608 H609 H641 H642 H643
H714 H721 H722 J0 J012 J013 J171 J172 J2 J271 J272 J371 J5 J581 L250
L432 M210 M211 M212 M213 M214 M215 M216 M231 M232 M233 M240 M262
M272 M273 M280 M281 M282 M283 M311 M312 M313 M314 M315 M321 M322
M331 M332 M333 M340 M342 M343 M344 M349 M371 M373 M381 M391 M392
M412 M413 M414 M415 M416 M510 M511 M512 M520 M521 M530 M531 M532
M533 M540 M541 M620 M710 M903

Ring Index Numbers: 00417; 00446; 00992